Chapter 24
Integration of Metabolism: Cellular Signaling

SUMMARY

Section 24.1

- All metabolic pathways are related, and some metabolites appear in several pathways.
- Many reactions of metabolism can take place simultaneously.
- The citric acid cycle plays a central role in metabolism, in both catabolic and anabolic pathways. The breakdown products of sugars, fatty acids, and amino acids all enter the citric acid cycle.

Section 24.2

- The sources of substrates for catabolism and for anabolism are the nutrients derived from foodstuffs.
- In humans, the choice of diet becomes important in the interest of obtaining enough of essential nutrients while avoiding excesses of others, such as saturated fats, where excess is known to play a role in the development of health problems.
- In 1992, a food guide pyramid was published to explain nutrition basics to the public. This pyramid is currently being replaced by a newer version that recognizes the differences between various types of fats and carbohydrates instead of just sending the message that all fats are bad and all carbohydrates are good.
- Obesity and Type 2 diabetes are lifestyle diseases that are reaching epidemic proportions in the United States.

Section 24.3

- Sophisticated fine tuning of metabolic processes in multicellular organisms is possible through the actions of hormones and second messengers.
- In humans, a complex hormonal system has evolved that requires releasing factors (under the control of the hypothalamus), trophic hormones (under the control of the pituitary), and specific hormones for target organs (under the control of endocrine glands).
- Feedback control occurs at every level of the system.
- One important system involves hormones that stimulate a membrane-bound G protein, which then stimulates adenylate cyclase to produce cAMP. In these cases, cAMP is the second messenger.
- In another important system, a hormone stimulates a different G protein that then stimulates phospholipase C. Phospholipase C converts phosphatidylinositol 4,5-bisphosphate (PIP_2) to diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3), both of which stimulate the opening of calcium channels and the release of Ca^{2+}. In this scenario, the Ca^{2+} is the second messenger.
- Receptor tyrosine kinases are a third important type of membrane protein involved in second messenger systems.

Section 24.4

- When a hormone binds to its receptor on the plasma membrane of a target cell, it sets off a cascade of reactions by which second messengers elicit the actual cellular response.
- Two of the most important second messengers, cyclic AMP (cAMP) and phosphatidylinositol- 4,5-*bis*phosphate (PIP_2), activate protein kinases, which phosphorylate key enzymes. Calcium ion is intimately involved in the action of PIP_2.
- Epinephrine stimulates adenylate cyclase in muscle cells, leading to activation of cAMP-dependent protein kinase. This ultimately leads to activation of glycogen phosphorylase and degradation of glycogen for energy.
- Glucagon stimulates adenylate cyclase in liver cells, leading to activation of cAMP-dependent protein kinase. This leads to inhibition of phosphofructokinase-2 and activation of fructose bisphosphatase-2. This lowers the level of fructose 2,6 – bisphosphate, which suppresses glycolysis and stimulates gluconeogenesis in the liver, leading to increased glucose production.
- Hormonal triggering can be added to other levels of control of metabolism, such as allosteric activation and covalent modification, to ensure an efficient response to the needs of the organism.

Section 24.5

- Insulin's primary job is to stimulate the glucose transporters in muscle —particularly the GLUT4 transporter—to take up glucose from the blood.
- In addition, it has a wide range of intracellular effects, such as switching off glycogen breakdown and turning on glycogen synthesis, stimulating glycolysis in the liver and muscle, turning off gluconeogenesis in the liver, and stimulating fatty-acid synthesis and storage.
- A recent discovery is that elevated levels of insulin in the blood may be related to Alzheimer's disease.
- Physical training appears to increase the sensitivity of the GLUT4 transporter to insulin such that an athlete needs less insulin to clear glucose out of the blood than a sedentary person.

LECTURE NOTES

The intent of this chapter is to tie together what students have already learned about metabolism by seeing how these concepts apply to nutrition, and hormonal control in a large-scale organism. The material in this chapter will take two to three lectures to cover.

LECTURE OUTLINE

I. Connections among metabolic pathways
II. Biochemistry and nutrition
  A. Required nutrients
    1. Macronutrients
    2. Micronutrients
  B. Food pyramid
  C. Obesity
III. Hormones and second messengers
  A. Hormones
  B. Second messengers
  C. Cyclic AMP and G proteins
  D. Calcium as a second messenger
  E. Receptor tyrosine kinases
IV. Hormonal control in metabolism
V. Insulin
  A. Structure
  B. Receptors
  C. Effect on glucose uptake
  D. Other enzyme effects
  E. Diabetes
  F. Insulin and sports

ANSWERS TO PROBLEMS

24.1 Connections between Metabolic Pathways

1. ATP and NADPH are the two molecules that link the most pathways.
2. Acetyl-CoA, pyruvate, PEP, α-ketoglutarate, succinyl-CoA, oxaloacetate, and several sugar phosphates, such as glucose-6-phosphate and fructose-6-phosphate.
3.

(a) Fructose-6-phosphate—from the pentose phosphate pathway (PPP).
(b) Oxaloacetate—to phosphoenolpyruvate in gluconeogenesis, to and from aspartate, to the glyoxylate cycle via citrate.
(c) Glucose-6-phosphate—to PPP, to and from glycogen in animals, to starch in plants.
(d) Acetyl-CoA—to and from fatty acids, to steroids (and isoprenoids), some amino acid degradations, to the glyoxylate cycle via citrate.
(e) Glyceraldehyde-3-phosphate—to reverse PPP.
(f) α-Ketoglutarate—to and from glutamate.
(g) Dihydroxyacetone phosphate—to and from the glycerol moiety of triacylglycerols and phosphoacylglycerols.
(h) Succinyl-CoA—degradation of fatty acids with odd numbers of carbon atoms, some amino acid degradation.
(i) 3-Phosphoglycerate—appears in the Calvin cycle.
(j) Fumarate—some amino acid degradations.

(k) Phosphoenolpyruvate—from oxaloacetate in gluconeogenesis.
(l) Citrate—to the glyoxylate cycle, transport across the mitochondrial membrane for fatty acid and steroid synthesis.
(m) Pyruvate—fermentation, to gluconeogenesis, also to and from alanine.

4. When the body breaks down proteins to supply material for gluconeogenesis, the increased urea output results in greater urine production, which uses water stored in the body. Fat metabolism also produces much metabolic water.

5.

(a) High ATP or NADH concentration and the citric acid cycle: isocitrate dehydrogenase (and the citric acid cycle) would be inhibited. The resulting pileup of acetyl-CoA (or citrate) would stimulate fatty acid and steroid synthesis, gluconeogenesis, and (in plants and some microorganisms) the glyoxylate cycle.
(b) High ATP concentration and glycolysis: phosphofructokinase-1 (and glycolysis) would be inhibited. Glucose-6-phosphate would pile up, stimulating glycogen (or starch) synthesis, the oxidative pentose phosphate pathway, or glucose formation. (c) High NADPH concentration and the pentose phosphate pathway: the oxidative branch of the pentose phosphate pathway would be inhibited, thus making glucose-6-phosphate available for other purposes. These include glycolysis, glycogen synthesis, glucose synthesis, and the “reverse” pentose phosphate pathway (yielding only pentose phosphate). (d) High fructose-2,6-*bis*phosphate concentration and gluconeogenesis: fructose-2,6-*bis*phosphate inhibits fructose-1,6-*bis*phosphatase and activates phosphofructokinase-1. Gluconeogenesis would thus be inhibited and glycolysis would be stimulated, as would the reverse pentose phosphate pathway and the production of glycerol phosphate for lipids.

6. Many compounds, such as oxaloacetate, pyruvate, and acetyl-CoA, play a role in a number of reactions. More to the point, the end products of some pathways are the starting points of others. Each pathway is one aspect of an overall metabolic scheme.
7. The *effect* of biochemical pathways can be reversed. Examples include glycolysis and gluconeogenesis, glycogen formation and synthesis, and the pentose phosphate pathway. The details are not completely reversible. An irreversible step in one pathway tends to be replaced with another reaction, catalyzed by another enzyme.
8. Transport processes are especially important for substances, such as oxaloacetate, that cannot cross the mitochondrial membrane. The same is true for electrons. Shuttle mechanisms must exist to transport electrons as the reduced form of important compounds. Compounds that cannot cross the membrane must be converted to ones that can, and then must be converted back to their original form on the other side of the membrane.
9. When a pathway has a number of steps, it is possible for energy changes to take place in steps of manageable size. It also allows for control of a pathway to be exercised at more points than would be the case if there were only a few steps.
10. The possibilities are limitless. Even more to the point, some discovery that no one expects can open even more possibilities.

24.2 Biochemistry and Nutrition

11. The old pyramid assumed that all carbohydrates and fats were the same and that carbohydrates were good and all fats were bad. The new pyramid recognizes that not all carbohydrates are good and not all fats are bad. Complex carbohydrates are placed lower down on the new pyramid, whereas processed ones are placed higher. Essential fats and oils are included as necessary food types. Also, dairy consumption recommendations have been reduced.
12. Fats and carbohydrates can be stored when they are consumed in excess. Fats are stored as triacylglycerols and carbohydrates are stored as glycogen. However, proteins consumed in excess are not stored. The extra protein is broken down. The amino groups are released as urea and the carbon skeletons are stored as carbohydrate or fat.
13. Saturated fatty acids have been correlated with increased levels of LDL, which have been shown to be an indicator of high risk for heart disease.
14. Leptin is a hormone that affects metabolism. It affects the brain to suppress appetite and it affects metabolism directly by stimulating fatty-acid oxidation and inhibiting fatty-acid synthesis.
15. Yes, cholecalciferol is made in the body, and many of its functions are hormone-like in nature.
16. Carbohydrates are the main energy source. Excess fat consumption can lead to the formation of “ketone bodies” and to atherosclerosis. Diets extremely high in protein can put a strain on the kidneys.
17. The liver is the primary organ for alcohol metabolism and for disposing of drugs (legal, illegal, and accidental) and halocarbon compounds. When the liver spends its time dealing with these other tasks, it may not be able to carry out its other normal functions; in essence, prolonged exposure to any such “toxin” overworks the liver.
18. Vitamin A is a lipid-soluble vitamin, which can accumulate in the body. Overdoses of this vitamin can be toxic.
19. Low levels of iodine in the diet often lead to hypothyroidism and an enlarged thyroid gland (goiter). This condition has largely been eliminated by the addition of sodium iodide to commercial table salt.
20. Lucullus breaks down the protein in the tuna to amino acids, which in turn undergo the urea cycle and the breakdown of the carbon skeleton described in Chapter 23, eventually leading to the citric acid cycle and electron transport. In addition to protein catabolism, Griselda breaks down the carbohydrates to sugars, which then undergo glycolysis and enter the citric acid cycle. (Gratuitous information: Lucullus was a notorious Roman gourmand. In medieval literature, Griselda was the name usually given to a forbearing, long-suffering woman.)
21. All amino acids must be present at the same time for protein synthesis to occur. Newly synthesized proteins are necessary for growth in the immature rats.
22. The weight loss is due to correction of the bloating caused by retention of liquids.

23. After a person is fully grown, many amino acids are scavenged and recycled by the body. Because all proteins contain at least some of these two amino acids, there are enough to maintain the body. It should be noted that both again become essential if there is disease or tissue damage and that arginine is required for sperm production in males.
24. The early colonists always cooked in iron pots; enough iron is leached out to supply required amounts, as long as the body is able to absorb it. (Glass cookware did not become available until after World War I, and aluminum cookware was not available until after World War II.)
25. Diets high in fiber are usually lower in fats, especially saturated fats; fiber adsorbs many potentially toxic substances, such as cholesterol and halocarbons, preventing their absorption into the body; fiber decreases transit time through the intestine, so any toxic materials in food remain in the body for less time and have a smaller chance of being absorbed or otherwise causing problems.
26. This claim has a chemical basis. Calcium carbonate dissolves in stomach acid, releasing calcium ion in its usual hydrated form. Calcium citrate is likely to have the calcium ion bound to the citrate in a manner similar to iron in heme. Consequently, the charge of the calcium ion is effectively decreased. Calcium bound to citrate can pass a cell membrane more easily than a hydrated calcium ion.
27. Alcohol provides calories but does not provide vitamins. This is one of the leading causes of malnutrition. Metabolizing alcohol involves an enzyme (alcohol dehydrogenase) with thiamine pyrophosphate (TPP) as a cofactor. The cofactor, in turn, is a metabolite of vitamin B_1, leading to severe deficiencies.
28. Metal ions play a role in the structure and function of proteins and some coenzymes. They tend to do so because they operate as Lewis acids.
29. Severe depletion of glycogen often results in a rebound effect, in which so much is made that some is stored in inappropriate tissues, including the heart, and mineral imbalances often occur. It is best to exercise moderately before the glycogen loading because then the glycogen is stored more effectively and safely in the liver and muscle tissue where it is most needed.
30. Nutrients and water turn over in the body, sometimes very frequently. This implies that an organism is an open system. Equilibrium requires a closed system. Consequently, an organism can reach a steady state, but never equilibrium.

24.3 Hormones and Second Messengers

31. Hormones can have several different kinds of chemical structures, including steroids, polypeptides, and amino acid derivatives.
32. The anterior pituitary stimulates release of trophic hormones, which in turn stimulate specific endocrine glands; the workings of the adrenal cortex, the thyroid, and the gonads can all be affected as a result. The adrenal cortex produces adrenocortical hormones, including glucocorticoids (involved in carbohydrate metabolism, inflammatory reactions, and reaction to stress) and mineralocorticoids, which control the level of excretion of water and salt by the kidney. If the adrenal cortex does not function adequately, one result is Addison’s

disease, characterized by hypoglycemia, weakness, and increased susceptibility to stress. The opposite condition, hyperadrenocorticism, is Cushing's syndrome.

33. The hypothalamus secretes hormone-releasing factors. Under the influence of these factors, the pituitary secretes trophic hormones, which act on specific endocrine glands. Individual hormones are then released by the specific endocrine glands.
34. Thyroxine is an amino acid derivative and is absorbed directly from the gut into the bloodstream. If insulin were taken orally, it would be hydrolyzed to amino acids in the stomach and intestine.
35. G proteins get their name because they bind GTP as part of their effect. An example is the G protein that is linked to the epinephrine receptor and leads to the production of cAMP as a second messenger. Receptor tyrosine kinases have a different mode of action. When they bind their hormone, they phosphorylate tyrosine residues on themselves and other target proteins, which then act as a second messenger. Insulin is an example of a hormone that binds to a receptor tyrosine kinase.
36. cAMP, Ca^{2+}, insulin receptor substrate.
37. Human growth hormone is a peptide hormone. If it were taken orally, the peptide would be degraded to its component amino acids in the small intestine and would be rendered useless.

24.4 Hormones and the Control of Metabolism

38. Epinephrine and glucagon are the two that were discussed the most in this book.
39. Glucagon causes the activation of glycogen phosphorylase, inhibition of glycogen synthase, and inhibition of phosphofructokinase-1.
40. Epinephrine has the same affect on glycogen phosphorylase and glycogen synthase, but it has the opposite effect on phosphofructokinase-1.
41. The G protein is bound to GTP. Eventually, the GTP is hydrolyzed to GDP, which causes it to dissociate from adenylate cyclase. This stops the hormone response until the hormone dissociates from the receptor, the G protein trimers are rejoined, and the process starts over again.
42. IP_3 is a polar compound and can dissolve in the aqueous environment of the cytosol; DAG is nonpolar and interacts with the side chains of the membrane phospholipids.
43. When a stimulatory hormone binds to its receptor on a cell surface, it stimulates the action of adenylate cyclase, mediated by the G protein. The cAMP that is produced elicits the desired effect on the cell by stimulating a kinase that phosphorylates a target enzyme.
44. See Table 24.2.
45. It is most unlikely that a metabolic pathway could exist without control mechanisms. Many pathways require energy, so it is advantageous for an organism to shut down a pathway when its products are not needed. Even if a pathway does not require large amounts of energy, the many connections among pathways make it likely that control is established over the levels of important metabolites.

46. In cholera, adenylate cyclase is permanently “turned on.” This in turn stimulates active transport of Na^+ and water from epithelial cells, leading to diarrhea.

47.
(a) Stoichiometric amounts of cAMP are required to activate cAMP-dependent protein kinase.
(b) Six catalytic steps, including the reaction catalyzed by glycogen phosphorylase, with 10 molecules acted on in each step, would result in 10^6 (one million) G-1-P molecules for each epinephrine.
(c) A major factor is speed. It is important to be able to use stored energy rapidly in “fight or flight” situations. A second factor is control. Note that glycogen phosphorylase is activated by kinases. The competing process of glycogen storage, catalyzed by glycogen synthetase, is inactivated by kinases. A third factor is economy. A single molecule of epinephrine activates many molecules of glycogen phosphorylase and yet more molecules of G-1-P.

48. A phosphatase dephosphorylates glycogen phosphorylase and glycogen synthetase, inactivating and activating them, respectively. The phosphatase becomes active in response to high concentrations of glucose.

49. Low-carbohydrate diets are designed to prevent the high blood sugar levels that arise when large quantities of carbohydrates are consumed. High blood sugar leads to a rapid rise in insulin. Insulin is known to stimulate fat synthesis and to inhibit fatty-acid oxidation. Thus, low-carbohydrate diets are thought to help fight weight gain.

24.5 Insulin and Its Effects

50. Insulin’s primary function is to stimulate the transport of glucose out of the blood and into the cell.

51. The second messenger is a protein called the insulin receptor substrate, which is phosphorylated on a tyrosine by the insulin receptor kinase.

52. When insulin binds to its receptor, the β-subunit of the receptor kinase autophosphorylates. When this happens, the receptor kinase is able to phosphorylate tyrosines on the insulin receptor kinase.

53. Insulin causes the following effects:
(a) Glycogen breakdown is decreased.
(b) Glycogen synthesis is increased.
(c) Glycolysis is increased.
(d) Fatty-acid synthesis is increased.
(e) Fatty-acid storage is increased.

54. Insulin and epinephrine normally have opposite effects, but they both stimulate muscle glycolysis. Epinephrine is the hormone that signals the need for quick energy, which means the muscle cells must be able to use glucose via glycolysis. Insulin stimulates pathways that use up glucose so that the blood glucose lowers, so it makes sense for it to stimulate glycolysis as well. Epinephrine stimulates muscle glycolysis by activating adenylate cyclase, which makes cAMP; cAMP then activates protein kinase A, which phosphorylates phosphofructokinase-2 and fructose-*bis*phosphatase-2. In the muscle, phosphorylation of phosphofructokinase-2 activates it, producing more fructose-2,6-*bis*phosphate, which activates phosphofructokinase-1 and glycolysis. In muscle, insulin stimulates glycolysis by activating phosphofructokinase and pyruvate dehydrogenase.
55. Prerace diet can be critical to a runner. If the race is at 9 AM, and the runner gets up at 7 AM and then eats a typical American breakfast of cereal, toast, or pancakes, she will have a high blood-sugar level within half an hour, which will lead to a high insulin level shortly thereafter. In that scenario, by the time the runner gets to the starting line, she will have a metabolism dedicated to fat and glycogen synthesis and will not be burning fat or carbohydrates. The runner will be like a car with a full tank of gas and a clogged fuel line.
56. It has been shown that the GLUT4 transporter responds to physical activity. When a person is active, the transporter is active and responds well to insulin. After a few days of detraining, this transporter shows only half of the activity it did before.
57. GLUT4 is one of the glucose transporters on muscle cells. It responds to insulin by moving glucose out of the blood and into the cell. In type II diabetes, insulin is present, but it does not have the same effect. It takes more insulin to accomplish the same movement out of the blood and into the cell. People with type II diabetes often show classical signs of obesity, and there is a correlation between diminishing GLUT4 activity, obesity, and diabetes.
58. Adipocytes, liver cells, and muscle cells.
59. Obese and diabetic individuals have a much higher risk of getting cancer than lean, healthy people, and when they do get cancer, their risk of dying from it is greater
60. The Warburg effect describes a situation where, when bathed in large amounts of glucose, and with significant insulin to allow the glucose to enter the cells, cancer cells adopt a strategy of running most of the glucose through anaerobic glycolysis. While energetically inefficient, anaerobic glycolysis avoids the loss of the carbon skeletons associated with aerobic metabolism.
61. Because of the link between some cancers, obesity, and diabetes, one can think of cancer as being a lifestyle disease as people that stay lean, fit, and healthy are therefore less likely to get cancer.
62. PTEN is a tumor suppressor gene often found to have been mutated in many cancers.
63. PTEN's role in tumor suppression appears to be via counteracting the action of PI_3 Kinase.